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Auditory spatial deficits in brainstem disorders

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ABSTRACT

Purpose: Brainstem disorders seem to negatively influence the central auditory system, causing spatial hearing deficits.

Material and methods: We tested 11 patients with brainstem lesions due to ischemic stroke (IS), multiple sclerosis (MS), or cerebellopontine angle tumor (CPAT) together with 50 age- and sex-matched healthy volunteers. We used pure tone audiometry (PTAud), brainstem auditory evoked potentials (BAEPs) and the horizontal minimum audible angle test (HMAAT) for 8 azimuths with binaural stimulation.

Results: The chosen patients and the controls had normal or near normal hearing in PTAud. BAEPs interaural wave I–V latency difference was over 7 times longer in the patients group compared to the controls. Additionally, 9 of the 11 patients (81.1%) had abnormal HMAAT results. The biggest quantitative disturbances in HMAAT were present in the CPAT and the MS patients. The sound localization ability in HMAAT was significantly worse in the patients in 0° azimuth in comparison with the controls, and in 45° and 90° azimuth in patients with auditory pathway involvement compared with the ones without the involvement.

Conclusions: Our study confirms the strong relationship between various brainstem pathologies and sound localization disability and sheds some light on the complexity of the relationship.

1. Introduction

Sound localization ability, or in other words directional hearing, was important for avoiding predators and thus is regarded as a phylogenetically older function than the reception of pure tones and understanding speech [1]. It is one of higher auditory functions and includes identification of distance, azimuth and directions of a moving sound in space

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Abbreviations: SPL, sound pressure level; HL, hearing level; HMAAT, the horizontal minimum audible angle test; BAEPs, brainstem auditory evoked potentials; PTA, pure tone average; PTAud, pure tone audiometry; kHz, kiloHertz; dB, decibel; ITD, interaural time delay; IID, interaural intensity delay; HRTFs, head-related transfer functions; IS, ischemic stroke; CPAT, cerebellopontine angle tumor; MS, multiple sclerosis; FDA, Food and Drug Administration; DCN, dorsal cochlear nucleus; VAS, ventral acoustic stria; TB, trapezoid body; SOC, superior olivary complex; LL, lateral lemniscus; IC, inferior colliculus.

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[2–4]. Giovanni Battista Venturi (1746–1822) is regarded as a forerunner of research on sound localization. He suspected that sound localization depends on asymmetry of the ears [5]. Brainstem anatomical structures responsible for proper sound localization seem to be active from birth [6]. The nuclei of the trapezoid corpus, nuclei of the lateral lemniscus, superior nucleus of the oliva and the nucleus of the inferior colliculus of the tectal lamina, constitute the basis of sound localization in the mechanism of interaural time delay (ITD), interaural intensity delay (IID) and head-related transfer functions (HRTFs) [7–9]. Pathological processes such as ischemic stroke (IS), demyelination in multiple sclerosis (MS) and cerebellopontine angle tumors (CPAT) can impair sound localization substantially because they restrict the broad stream of information going to the upper levels of the central nervous system (CNS) [2,10–15]. However, brainstem pathology is not the only reason for disturbed sound localization. The cortical sound localization centers are localized in the temporal, the parietal and the frontal lobes and pathological processes of theses regions can also substantially disturb the sound localization ability [2,4,16]. Since Venturi's time scientists have been trying to explain complicated neuronal mechanisms of sound localization. Research on sound localization in patients with brainstem pathologies showed a correlation between lesion localization and disturbed binaural auditory tasks. The correlation was particularly strong if the pathological process took place in the inferior colliculus and the lateral lemniscus [13,17,18]. However, results of the studies are inconsistent as far as the influence of side and volume of a lesion on sound localization ability is concerned. Additionally, the high redundancy of brainstem structures of the auditory pathways and the diversity of neuronal networks are the reason for small pathological lesions of these regions to be often clinically silent. The primary aim of this study was to find spatial hearing deficits characteristic for different brainstem pathologies. Secondly, we aimed to investigate a putative correlation between the side and the level of auditory pathway involvement in the MRI and the type of sound localization disturbance.

2. Methods

2.1. Patients

34 patients with brainstem pathology were included in the study. They were patients of the Neurology Outpatient Clinic, the Department of Neurology, the Audiology Outpatient Clinic or the Department of Otolaryngology, in years 2006–2011. Hearing tests were performed in the Audiology Outpatient Department. All patients underwent the pure tone audiometry (PTAud), the brainstem auditory evoked potentials (BAEPs) and the horizontal minimum audible angle (HMAAT) testing. The most important exclusion criteria for the study was the interaural difference of hearing threshold for medium frequencies-pure tone average (PTA-0.5–1–2 kHz) $>$ 20 dB HL and contraindications for the head MRI. Additional exclusion criteria were: age older than 80 years, patients with previous history of stroke (but not transient ischemic attack), serious general state, dementia, neurodegenerative disorders, other previously identified neurological diseases, patients without logical verbal contact due to aphasia, psychotic symptoms, visual spatial neglect syndrome tested with the line bisection test and the nonverbal shape cancelation task [19,20], conductive or mixed type hearing loss, history of ear surgery. Due to the abovementioned criteria we included 11 patients in the analysis. There were 4 ischemic stroke (IS) patients (2 women and 2 men). All subjects were right-handed. All neurootologic evaluations were performed during the early stage after the incidence of stroke (up to 30 days, average 10 $\pm$ 7 days). The diagnosis of stroke was based on the WHO criteria in patients with neurologic symptoms lasting for at least 24 h. We excluded patients with ischemic lesions localized in the hemispheres. There were 5 patients with multiple sclerosis (3 women and 2 men) in the group. The diagnosis of MS was based on the McDonald et al. [21] criteria. We excluded patients with demyelinating lesions affecting the hemispheric part of the auditory pathway. All neurootologic evaluations were performed 2 months to 12 years from first MS symptoms. Only two patients from the study group suffered from cerebellopontine angle tumor (CPAT) (1 woman and 1 man). The diagnosis was based on the criteria of Kanzaki et al. [22]. The study was approved by the regional independent ethics committee (NKEB/32/2006). All the patients and the control subjects provided written, informed consent for involvement in the study.

2.2. Controls

The control group consisted of 50 age-matched subjects, 19 men and 31 women (on average 4.6 controls per one patient). The average age of the group was 50.1 (SD $\pm$ 17.4) years (range 21–80 years) and it consisted of healthy volunteers. The exclusion criteria for the control group were: previously identified neurological diseases, diabetes, circulatory insufficiency, alcoholism, smoking, use of medications affecting the CNS, history of noise exposure at work, hearing disorders including the conductive and the mixed type hearing loss, and history of ear surgery. All subjects underwent otological and neurological examination. We also excluded patients with abnormal BAEPs results. According to the Food and Drug Administration (FDA) classification [23] 3 subjects had sensorineural mild hearing loss. All of them were over 60 years of age and their hearing loss was due to cochlear presbyacusis.

2.3. Study design

A detailed protocol was developed prior to conducting this study. Randomly selected neurological patients and matched controls were examined for peripheral and central hearing deficits by an independent audiologist in a standard case–control study fashion.

2.4. Localization of brainstem lesions in the MRI

All patients underwent magnetic resonance imaging (MRI) of the brain according to standard imaging protocols in 1.5T scanners. Determination of areas of focal brain damage was performed manually based on supplied imaging data sets. Localization of the lesions and involvement of the structures

of the auditory pathway were co-registered with use of multiplanar anatomical atlas for radiologists and surgeons [24]. In case of two patients with cerebellopontine angle tumors a typical appearance of enhancing extra-axial lesions was conclusive for the diagnosis. In case of brainstem lesions in MS and IS patients a region of abnormally high signal in T2-weighted images was considered a lesion if it was found and confirmed within the corresponding horizontal, coronal and parasagittal planes. In all images that a lesion appeared in the axial plane, it was outlined, in order to form a 3-D model. Next, the model was used to calculate volume of the lesion with use of the StealthViz surgical planning software (Medtronic Inc., Minneapolis, USA). StealthViz is approved and registered for medical use by Food and Drug Administration. In case of multiple lesions (MS patients – Table 2), a lesion localized in the auditory pathway or the biggest lesion of the brainstem was chosen for volume calculation.

2.5. *Hearing tests*

Hearing tests were performed within 4 months from the MRI scan (within one week to 4 months; 2 months on average).

2.5.1. *Pure tone audiometry (PTAud)*

The standard tonal audiometry in a soundproof booth was performed in all of the study subjects. Signals were generated by calibrated clinical audiometers: Midimate 622, manufactured by Madsen Electronics (Otometrics, Copenhagen, Denmark). The equipment had corrections for standard hearing level – ISO-389-1: 1998 for the air conduction, and ISO-389-3: 1994, for the bone conduction. For the air conduction testing, the electrical signal was generated by the audiometer coupled with TDH-39P headphones. For bone conduction testing, the audiometer was coupled to a radioear B-71 bone-conduction vibrator (New Eagle, PA). The audiometric values are averages of values at 500, 1000, 2000 and 4000 Hz. We excluded patients from the study if they presented asymmetrical hearing loss – if the difference between the ears was >15 dB HL (hearing level). If the hearing threshold for frequencies 500–1000–2000–4000 Hz was >20 dB HL in one ear, the unilateral hearing loss was diagnosed, if in both ears – bilateral hearing loss (with the differences ≤15 dB HL between the ears in both situations).

2.5.2. *Brainstem auditory evoked potentials (BAEPs)*

This test was performed in a recumbent position in a soundproof studio with a Centor-C equipment (RACIA-ALVAR). In order to receive the brainstem potentials electrodes were placed in a standard position – 2 electrodes in the retroauricular areas, one on the forehead and one on the right cheek. The potentials were evoked by an unfiltered 10 Hz click lasting for 100 μs. TDH-39 headphones were used to produce the click alternately. The untested ear was masked with white noise 30 dB lower than the click. The intensity of the click was set on 80 dB HL. Each ear was tested twice. Low-pass filter of 1600 Hz and high-pass filter of 160 Hz was used in the amplifier during the analysis of the biological signal. Each averaged response represented 1600 repetitions. If the morphology of waves was distorted, the potentials for 90, 100 and 110 dB were tested. We analyzed the morphology of waves, the presence or absence of waves I–V, the latency of wave I, III and V, and the interaural wave I–III and I–V latency difference. Extracochlear hearing loss was diagnosed in cases with the interaural wave I–III and/or I–V latency difference >0.2 ms. Normal ranges for BAEPs: wave I latency ≤1.9 ms, wave V latency ≤6.2 ms, interval I–III ≤2.6 ms, interval III–V ≤2.4 ms, interval I–V ≤4.6 ms, interaural interval difference ≤0.2 ms, interaural wave V latency difference ≤0.4 ms, wave V/I quotient ≥1.5 [25]. Interaural interval difference is a difference between the I–V interval of the left and right ear calculated in ms. In cases of extracochlear disturbance present only in one ear, with normal hearing threshold and normal potentials of the opposite ear, the potentials of the normal ear were treated as the reference range.

2.5.3. *Horizontal minimum audible angle test (HMAAT)*

For estimation of the horizontal minimum audible angle the wide-band noise bursts were used between 80 and 12,500 Hz. The signal was presented in two sets of 1-s bursts, separated by 2.5 seconds with rise-fall times of 50 ms. Finally, a 4.5 s pause finished the cycle. The acoustic pressure level of these bursts was 85 dB SPL. Signals were reproduced from CD player and after amplification transmitted to the loudspeaker attached to a metal arm installed to the ceiling of the study room. The laser pointer was attached to this arm which showed its displacement every 1° on the scaled table installed on the ceiling. The distance from the loudspeaker to the subject's head was fixed at 50 cm. During the test the subject was seated on the metal armchair with his head immobilized by a metal headholder and was blind-folded. The measurement was made in the free-field in the horizontal plane at eight equally spaced angles (every 45°) around the head for the azimuths: 0°, 45°, 90°, 135°, 180°, 225°, 270°, 315° and each time the average angular value was calculated. For the 0° azimuth the loudspeaker was positioned in front, for 45° azimuth on the right side, for 180° azimuth behind and for 270° azimuth on the left side of the tested person's head. The test was started from 0° azimuth onward (counter-clockwise) and finished on 315° azimuth. At each of all the 8 azimuths measurements were made with a movement of the sound source to the right and to the left, and the final result was the arithmetic mean value of both of these results, as in the method proposed by Mills [26]. Each test was started by a short training at 0° azimuth with eyes open and then closed. The examined person was instructed to inform verbally ''from two places'' vs. ''from one place'' after the second signal was generated in another point of space. That value of angles was noted in a special form as the minimum audible angle (MAA) for each azimuth (on the right, on the left, final MMA). The MAA was measured at each of the 8 azimuths.

The upper limit of the reference range was set at the 95th percentile of the results received in the control group divided into 5 age subgroups (21–30; 31–40; 41–50; 51–60; 61–70) (Table 1 and Fig. 1). Results obtained in the tested group were considered abnormal if they exceeded the reference range for at least one of the azimuths. In case of abnormal MAA value measured for at least two of 45°, 90° and 135° azimuths the result was considered as the right-sided unilateral abnormal result of the test, and for 225°, 270° and 315° azimuths the result was considered as the left-sided unilateral abnormal result. The reference ranges presented by Kruk-Zagajewska [27] for HMAAT were slightly higher for the 95th percentile for

Table 1 – Reference HMAAT values in age subgroups (values for 95th percentile).

Age groups	Control group HMAAT results							
	0°	45°	90°	135°	180°	225°	270°	315°
21–30	4.3	5.8	7.4	7.7	7.9	6.3	7.8	5.9
31–40	4.7	6.8	8.8	8.0	6.6	7.3	7.8	7.0
41–50	6.9	9.0	12.9	13.9	8.9	9.9	14.1	8.7
51–60	5.8	10.1	14.0	10.0	10.0	9.8	14.8	9.0
61–70	8.0	15.3	16.0	15.8	11.0	11.3	14.8	14.0
71–80	9.1	15.0	16.5	16.1	11.0	11.5	15.1	14.3

all age subgroups, especially for 0° azimuth. However, Kruk-Zagajewska used 1 kHz pure tone for stimulation, which is more selective in auditory activation than the wide-band noise used in our study. Häusler et al. [2], who used wide-band noise stimulus in volunteers (age 8–68) with normal hearing, received similar MAA results to ours.

2.6. *Data analysis*

The correctness of matching subjects with controls was verified by means of conditional logistic regression (StatsDirect Ltd.; Cheshire, UK), a method adjusting simultaneously for multiple confounders (in our study: binary variable – sex and continuous variable – age). Mean value and standard deviation (SD) were provided in descriptive statistics throughout the study. The analysis was carried out with the chi-square with or without Yates correction, the *U*-Mann–Whitney test for independent groups and the ANOVA Kruskal–Wallis test. Statistical analysis was performed using Statistica v.10.0 (StatSoft; Tulsa, OK, USA). Values of $p < 0.05$ were considered significant.

3. Results

Epidemiological data, side and localization of lesions, involvement of the auditory pathways in the MRI, BAEPs and PTAud results of the patients are presented in Table 2. HMAAT for the 8 azimuths are presented in Table 3.

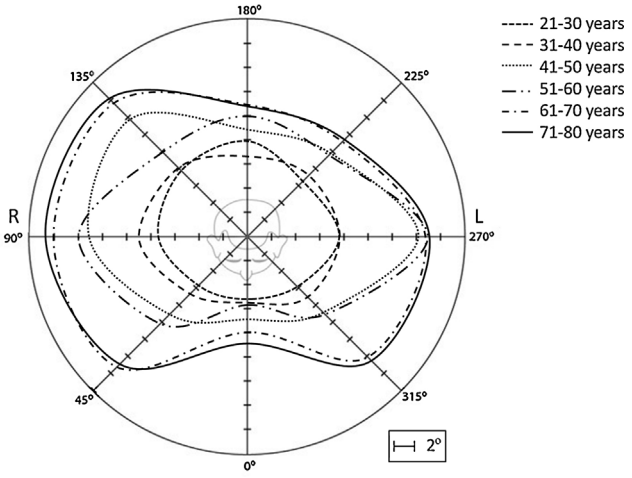

Fig. 1 – HMAAT values for 95th percentile in 6 age subgroups of the control group with normal hearing. These values were used as reference values. R – right side; L – left side; azymuth 0° – frontal; 180° – occipital. 2° scale was used to present HMAAT values in each azimuth.

3.1. *Tonal audiometry results*

Mean PTA value for the study group was 14.9 (±SD 9.7) dB HL, while for the control group 10.8 (±SD 6.2). The differences were not statistically significant ($p > 0.05$; $U = 261$ in Mann–Whitney test).

3.2. *BAEPs*

Raw data on latency of wave I, II and V, intervals I–III and I–V, interaural latency I–V differences and amplitudes of wave I

Table 2 – Epidemiological data, side and localization of lesions, involvement of the auditory pathways in MRI and BAEPs studies together with PTA results in the IS, MS and CPAT patients.

No.	Age	Sex	Pathology	Side of the lesion	Lesion location	Involvement of the auditory pathway MRI	Single/ multiple lesion	V [mL]	Involvement of the auditory pathway BAEPs	PTA right	PTA left
1	21	F	IS	R	Pon	NAPI	S	1.19	N	10.0	11.7
2	68	F	IS	R	Pon	SOC	S	1.22	N	23.3	18.3
3	54	M	IS	R	Pon	VCN, VAS	S	3.12	N	18.3	18.3
4	52	M	IS	R	MO	DCN	S	0.17	Brainstem$^{V\ ampl.}$	26.7	23.3
5	27	M	MS	R	Pon	VCN	M	0.02	Brainstem$^{III–V}$	20.0	21.7
6	30	F	MS	L	Pon	NAPI	M	0.05	CN VIII$^{I–III}$	1.7	1.7
7	28	M	MS	L	Pon	IC	S	0.02	CN VIII$^{I–III}$	0.0	5.0
8	37	M	MS	L	Pon	NAPI	S	0.03	Brainstem$^{III–V}$	8.3	10.0
9	41	F	MS	R	MO	VCN	M	0.17	N	10.0	3.3
10	40	F	CPAT	R	CN VIII	CN VIII	S	4.19	CN VIII$^{I–III}$	31.7	31.7
11	42	F	CPAT	R	CN VIII	CN VIII	S	0.04	N	23.3	11.6

Abbreviations: BAEPs – brainstem auditory evoked potentials; CN VIII – cranial nerve VIII; CPAT – cerebello-pontine angle tumor; DCN – dorsal cochlear nucleus; F – female; M – male; V – volume of the brainstem lesion; HMAAT – horizontal minimum audible angle test; IC – inferior colliculus; IS – ischemic stroke; MO – medulla oblongata; MS – multiple sclerosis; N – normal; NAPI – no auditory pathway involvement; Pon – Pons; PTA – pure tone average (mean for 0.5–1–2 kHz dBHL); SOC – superior olivary complex; VAS – ventral acoustic stria; VCN – ventral cochlear nucleus; V ampl. – reduction of wave V amplitude (ratio of I/V amplitudes ≤1); III–V – elongation of III–V interval; I–III – elongation of I–III interval.

Table 3 – HMAAT results in the IS, MS and CPAT patients.

No.	Abnormal HMAAT	HMAAT results							
	Yes or no	0°	45°	90°	135°	180°	225°	270°	315°
1	No	3.0	1.5	3.5	1.0	1.5	2.5	3.0	2.0
2	Yes	18.0[a]	6.5	29.0[a]	17.0	25.0[a]	25.0[a]	30.0[a]	24.0[a]
3	Yes	13.5[a]	24.0[a]	44.0[a]	4.5	5.0	13.0[a]	38.0[a]	5.0
4	Yes	9.0[a]	7.0	9.5	4.0	3.0	4.5	5.0	11.0[a]
5	Yes	8.0[a]	15.0[a]	13.0[a]	13.0[a]	8.0	6.0	3.0	5.0
6	No	3.0	3.0	1.5	3.5	1.0	1.5	2.5	3.0
7	Yes	6.5[a]	11.0[a]	6.0	11.0[a]	9.0[a]	7.0[a]	5.0	3.0
8	Yes	8.0[a]	7.0	9.0	6.0	8.0[a]	13.0[a]	15.0[a]	13.0[a]
9	Yes	8.0	15.0[a]	13.0[a]	13.0[a]	8.0	6.0	3.0	5.0
10	Yes	13.0[a]	13.0[a]	19.0[a]	3.0	1.0	1.0	11.0[a]	5.0
11	Yes	9.0[a]	10.0[a]	22.0[a]	13.0	8.0	9.5	11.5	6.5

[a] Abnormal value of HMAAT [°] as ≥95th percentile of the results received in the control group divided into 5 age subgroups (21–30; 31–40; 41–50; 51–60; 61–70 years).

and V are presented in Table 4. Abnormal BAEPs were present in 6 (54.4%) patients. Three of them had elongated I–III interval, two of them elongated III–V interval and one presented decreased amplitude of wave V. In all of the 6 patients the interaural wave I–V latency difference was >0.2 ms. The BAEPs interaural wave I–V latency difference was over seven times longer in the patients group 0.75 (±SD 0.87) in comparison with the control group – 0.10 (±SD 0.09) ($p = 0.002$; $U = 137$ in Mann–Whitney test). The highest values were present in the MS patients – 1.31 (±SD 1.04), and the lowest in the CPAT patients – 0.67 (±SD 0.00) (Kruskal–Wallis, $p = 0.001$). There was no correlation between the level of damage of the brainstem auditory pathway in the MRI and the BAEPs (Pearson's chi-squared test with Yates correction, $p = 0.320$).

3.3. *Cross-sectional HMAAT analysis*

Table 5 presents average angular values for chosen azimuths in the HMAAT in the study and control group and in patients with or without auditory pathways involvement. Statistically significant differences in average HMAAT results between the patients and the controls were found only for 0° azimuth (Table 5). Comparison of HMAAT results of patients with MRI confirmed auditory pathway involvement ($N = 8$) with patients without this involvement ($N = 3$) proved the biggest differences for 90° and 270° azimuths. However, we found statistically significant difference only for 90° azimuth between the patients with and without auditory pathways involvement ($p < 0.05$ for correlation coefficient). Additionally, we calculated correlation coefficients between HMAAT results and lesion volume for all of the azimuths. We found statistically significant correlation between the lesion volume and the HMAAT value [°] for 2 azimuths – 90° and 270° ($p < 0.05$ for correlation coefficient).

3.4. *Affected azimuths in the HMAAT*

9 patients (81.1%) had abnormal HMAAT results at least in 2–6 azimuths. Only 2 of them (18.9%) (one IS and one MS patient) presented normal sound localization ability. Both patients had the lesion localized in the pons (Fig. 1). Abnormal HMAAT results were most common in the right-sided and front azimuths – 0°, 45° and 90° (9 patients). The 180°, 225° and 315° azimuths were affected least often (6 patients).

3.5. *HMAAT results and types of brainstem lesions*

The worst results, as far as the number of affected azimuths is concerned, were found in the CPAT patients – 3.5 (±SD 0.70)

Table 4 – BAEPs latencies, interlatencies and amplitudes of the patients with brainstem pathology.

No.	Latencies (ms)						Interlatencies (ms)							Amplitudes (μV)	
	I (R)	III (R)	V (R)	I (L)	III (L)	V (L)	I–III (R)	I–V (R)	III–V (R)	I–III (L)	I–V (L)	III–V (L)	Interaural I–V latency difference	I/V (R)	I/V (L)
1	1.77	3.65	5.25	1.70	3.65	5.15	1.88	3.47	1.60	1.95	3.45	1.50	0.02	0.30/0.66	0.21/0.48
2	1.82	3.57	5.80	1.60	3.82	5.75	1.92	3.97	2.05	2.22	4.15	1.92	0.18	0.15/0.52	0.22/0.30
3	2.00	4.52	6.70	1.95	4.38	6.70	2.52	4.70	2.17	2.42	4.75	2.33	0.05	0.12/0.26	0.06/0.17
4	2.10	4.25	6.15	2.15	4.35	6.05	2.15	4.05	1.90	2.20	3.90	1.70	0.15	0.34/0.17	0.11/0.28
5	1.45	4.10	6.00	1.25	4.20	8.05	2.65	4.55	1.90	2.95	6.80	3.85	2.25	0.19/0.28	0.11/0.23
6	1.75	3.65	5.85	1.70	6.75	8.20	1.90	4.10	2.20	5.05	6.50	1.45	2.40	0.09/0.17	0.11/0.15
7	1.55	3.85	5.80	1.80	5.30	7.45	2.30	4.25	1.95	3.50	5.65	2.15	1.40	0.09/0.24	0.15/0.34
8	1.7	3.95	6.05	1.85	4.15	5.85	2.25	4.35	2.10	2.30	4.00	1.70	0.35	0.15/0.26	0.22/0.41
9	1.25	3.75	5.85	1.35	3.65	5.80	2.50	4.60	2.10	2.30	4.45	2.15	0.15	0.24/0.42	0.46/0.66
10	1.67	3.83	5.70	1.80	3.55	5.35	2.15	4.03	1.88	1.75	3.55	1.80	0.48	0.25/0.83	0.28/0.87
11	1.58	3.60	5.50	1.45	3.58	5.45	2.03	3.92	1.90	2.13	4.00	1.88	0.07	0.23/0.39	0.29/0.48

Table 5 – Average angular values for chosen azimuths in the HMAAT in the study and the control group and in patients with or without auditory pathways involvement.

HMAAT	Patients with brainstem lesions (N = 11)	Controls (N = 50)	p value (Mann–Whitney test)	Patients with auditory pathway involvement (MRI) (N = 8)	Patients with intact auditory pathway (MRI) (N = 3)	p value (Mann–Whitney test)	Correlation coefficient for HMAAT result and lesion volume	p value (for correlation coefficient)
Azimuths	Mean (±SD)	Mean (±SD)		Mean (±SD)	Mean (±SD)			
0°	**8.9 (4.4)**	**4.5 (2.6)**	**<0.001**[a]	10.6 (3.8)	4.7 (2.9)	NS	0.3752	NS
45°	10.3 (6.4)	7.4 (4.4)	NS	**12.7 (5.6)**	**3.8 (2.8)**	**0.041**[a]	0.4472	NS
90°	15.4 (12.5)	9.6 (4.7)	NS	**19.4 (12.3)**	**4.7 (3.9)**	**0.032**[a]	**0.7352**	**0.01**[a]
135°	8.0 (5.4)	8.4 (4.6)	NS	9.6 (5.3)	3.5 (2.5)	NS	0.1874	NS
180°	7.0 (6.7)	6.5 (2.9)	NS	8.4 (7.3)	3.5 (3.9)	NS	0.1260	NS
225°	8.1 (6.9)	6.9 (2.6)	NS	9.0 (7.3)	5.7 (6.4)	NS	0.4153	NS
270°	11.2 (12.1)	9.3 (4.2)	NS	12.9 (13.5)	6.8 (7.1)	NS	**0.7989**	**0.003**[a]
315°	7.5 (6.4)	7.3 (4.4)	NS	8.1 (6.8)	6.0 (6.1)	NS	0.0900	NS

[a] Statistical significance (Pearson's chi-squared test ± Yates correction); NS – statistically non-significant.

azimuths. The MS patients had only slightly better results – 3.4 (±SD 2.07) azimuths. The IS patients had the best results in the patients group – 3.0 (±SD 2.94) azimuths. In case of lesions localized in the VIII cranial nerves and the medulla oblongata the mean number of altered azimuths was 2.75 (±SD 1.25). Lesions localized in the pons correlated with higher number of affected azimuths – 4.0 (±SD 2.34).

3.6. *HMAAT, BAEPs and auditory pathway involvement*

In 8 of 9 (88.9%) patients with abnormal HMAAT results, and in 5 of 7 (71.4%) who presented abnormal BAEP results, the results/symptoms corresponded to pathological involvement of the auditory pathway observed in the respective MRI studies. However, these correlations were not statistically significant (Pearson's chi-squared test with Yates correction, $p = 0.093$ and $p = 0.564$ respectively). Analysis of the correlation between the abnormal HMAAT and BAEPs results proved no significant correlations for the specific azimuths ($p \leq 0.185 \geq 0.893$ for correlation coefficient).

3.7. *HMAAT and the level of brainstem pathology*

We compared sides of the sound localization disturbance and the level of auditory pathway disruption in the brainstem. Patients with lesions localized below the level of the ventral acoustic stria (VAS) (the ventral acoustic nucleus, VCN, cranial nerve VIII, CNVIII) ($n = 6$) had ipsilateral sound localization disturbances in 4 cases, contralateral in 1 case and bilateral in 1 case. In cases of lesions localized higher in the brainstem (the superior olivary complex, SOC; the lateral lemnicus, LL; and the inferior colliculus, IC) all patients ($n = 2$) had contralateral disturbances of sound localization. Fig. 2 presents HMAAT result of a patient with the auditory pathway distorted in the VAS area. The frontal 0° and 315° azimuths were affected. Fig. 3 presents ipsilateral sound localization disturbance in a patient with auditory pathway ivolvement below the VAS (the cochlear nerve). In this case the right-sided CPAT correlated with abnormal results in the right-sided 45°, 90° and 0° azimuths (Fig. 4).

4. Discussion

To understand the relationship between brainstem lesions and auditory dysfunction in patients with ischemic stroke, multiple sclerosis and cerebellopontine angle tumors, we compared results of the head MRI, the BAEPs, and the HMAAT in 11 patients with normal or near normal hearing.

Normal hearing is rare in patients with brainstem pathologies, especially in patients with cerebellopontine tumors. However, hearing asymmetry and all other kinds of hearing loss can disturb the sound localization ability. Thus, we decided to create a study group that would have normal hearing and that would not differ in PTAud results from the control group. Similar approach can be observed in many of the previous studies in this subject [13,17,28]. However, in some studies the PTAud methodology was less restrictive [2,14].

The BAEPs were abnormal in 6 patients. Four of the patients with abnormal BAEPs presented auditory pathway involvement. The other 5 patients had normal BAEPs even though they also presented the auditory pathway involvement in the MRI, mainly on the level of the pons. Thus, it seems that BAEPs can remain normal in cases of auditory pathways involvement on the level of the trapezoid body or the lateral lemniscus. Pratt et al. [29] used binaural BAEPs, in contrast to our monaural BAEPs. They used binaural interaction components (BICs) in the latency range of peaks IV–VI, which was supposed to increase the possibility of detection small pontine lesions. They obtained BICs by subtracting the binaurally evoked potentials from the algebraic sum of the monaurally evoked potentials for each of the 3 channels, using the formula: (left monaural + right monaural) – binaural.

Levine et al. [28] suggested that BAEPs are less sensitive indicator of auditory dysfunction than the ITD, with the difference between the tests of more than 30%. Although our HMAAT method is different from the one used by Levine et al. [28], the HMAAT results depend at least partially on the ITD and IID mechanisms. In our study the difference between abnormal HMAAT results (88.9%) and BAEPs results (71.4%)

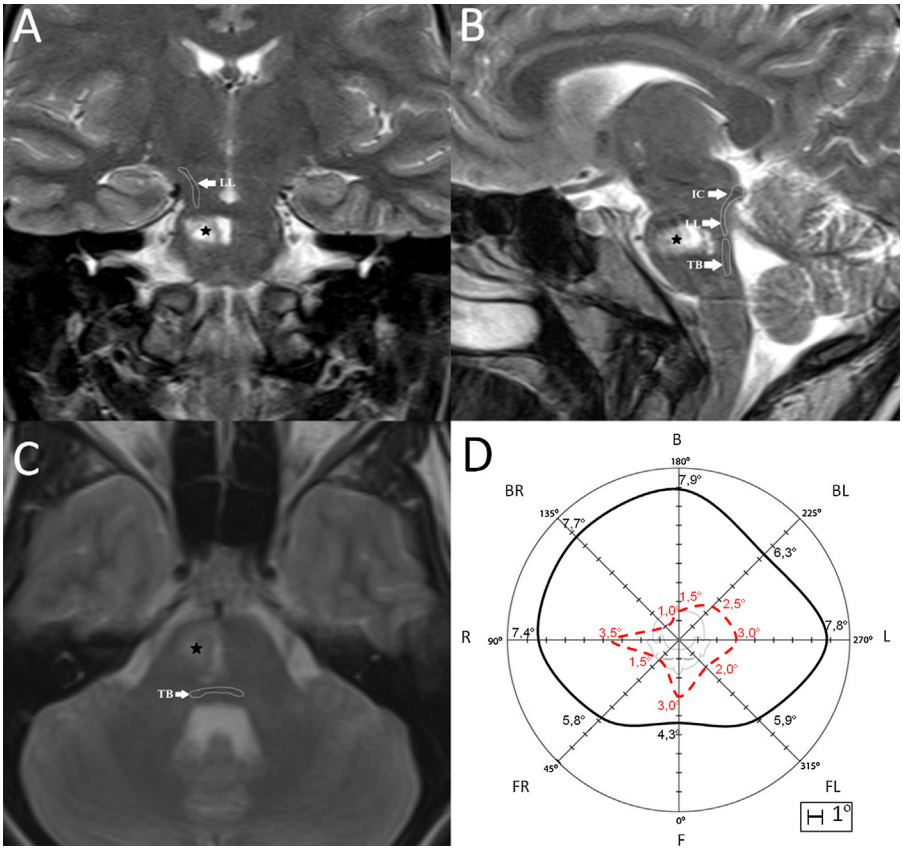

Fig. 2 – A 21-yo female patient. Magnetic resonance images of the ischemic brainstem lesion (black star) in coronal (A), sagittal (B) and axial (C) planes show no visible involvement of the auditory pathway structures (white outline). (A) Arrow points at the lateral lemniscus (LL). (B) Arrows point at the inferior colliculus (IC), the lateral lemniscus (LL) and the trapezoid body (TB) respectively. (C) Arrow points at the trapezoid body (TB). The HMAAT results (D). Black line – 95th percentile values for the age-matched subgroup of controls, red dotted line – results of the patient. F – front; B – back; R – right; L – left; FR – frontal right; FL – frontal left; BR – back right; BL – back left. Red color – actual data points for MAA angle value in a patient; black color – reference value of respective age subgroup. *MAA values exceeding 95th percentile values for the age-matched subgroup of controls. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

was 17.5%, which proves higher sensitivity of HMAAT. However, it seems reasonable to assess extracochlear hearing loss in cases of brainstem pathology with combination of HMAAT and BAEPs.

Brainstem pathologies in our patients caused substantial elongation of the microphonic cochlear potentials (I–V interval). We found the longest interval in the MS patients – the interval was twice as long the one in the CPAT patients. Both MS and CPAT can reduce the conduction velocity of auditory evoked potentials but in different mechanisms. MS causes reduction of the conduction velocity inside the brainstem [18], while CPATs reduce the velocity due to pressure on the VIII nerve.

Häusler et al. [2] and Levine et al. [28] noticed that MS patients that had incorrect BAEPs responses on at least one side, also had abnormal ITD results. Furst et al. [18] made similar observations in their MS patients. Levine et al. [30] suggested that wave V in BAEPs test represents a pontine time comparator such as the medial superior olive, which sends projections to such structures as the lateral lemniscus. They found that ITD disturbance for high-frequency noises always coexists with unilateral V wave disturbance in the BAEPs but not always with unilateral disturbance of latency of this wave [14]. In our study we found only one case (patient No. 4, Table 4), where amplitude of wave I was higher than of wave V (normally amplitude of wave V is higher than of wave I), and it coexisted with sound localization disturbance in anterior azimuths (Fig. 2). Only few of our patients presented sound localization disturbances that accompanied the elongation of the V wave latency.

We found sound localization disturbances in 9 of our 11 patients (81.1%). Sound localization disturbances were also very common in a study by Levine et al. [28].

There have been no studies so far that would correlate brainstem pathologies with the severity of the sound localization disturbance. It was the influence of localization of pathology that was studied most. We obtained the worst HMAAT results in the CPAT patients (with 3.5 azimuths being affected on average). Walsh [15] noticed in experiments with ‘‘diotic stimulation’’ and exclusion of vision, that only few

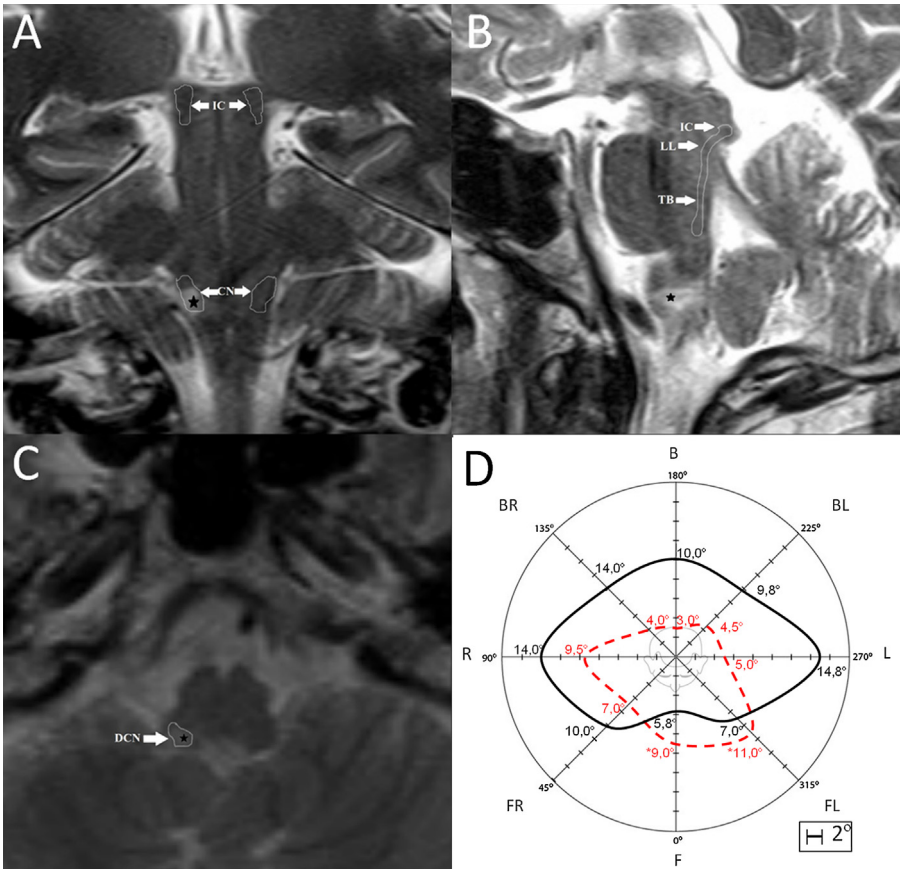

Fig. 3 – A 52-yo male patient. Magnetic resonance images of the ischemic brainstem lesion (black star) in coronal (A), sagittal (B) and axial (C) planes show involvement of the auditory pathway structures (white outlines) at the level of the right dorsal cochlear nucleus (DCN). (A) Arrows point at the inferior colliculi (IC) and the cochlear nuclei (CN). (B) Arrows point at the inferior colliculus (IC), the lateral lemniscus (LL) and the trapezoid body (TB) respectively. (C) Arrow points at the right dorsal cochlear nucleus (DCN). The HMAAT results (D). Black line – 95th percentile values for the age-matched subgroup of controls, red dotted line – abnormal results of the patient in the 0° and 315° azimuths. F – front; B – back; R – right; L – left; FR – frontal right; FL – frontal left; BR – back right; BL – back left. Red color – actual data points for MAA angle value in a patient; black color – reference value of respective age subgroup. *MAA values exceeding 95th percentile values for the age-matched subgroup of controls. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

patients with brainstem lesions had worse results in the horizontal sound localization, if the reason was MS. However, all the patients could not localize the sound properly in the vertical plane. Häusler et al. [2] studied 26 patients with MS, age range 16–58 years, and found good frontal localization and changeable results for sides (normal to substantially distorted) but they did not report how many of the patients had demyelinating lesions in the brainstem. Patients with MS tend to have multiple scattered lesions some of which could include brainstem regions involved in sound localization. Some of our MS patients had multiple lesions in the brainstem, and in case of 2 of 3 subjects with multiple lesions (subject 5 and 9, see Table 2), we managed to prove the auditory pathway involvement in the MRI on the level of VCN with abnormal sound localization. However, 4 of 5 patients with MS had abnormal BAEPs with abnormal sound localization (Tables 2 and 3). According to Furst et al. [18], in a demyelinatined lesion the neural impulses are conducted through the lesion but at a reduced conduction velocity. It was suggested that the pathology on the level of the VIII nerve does not always have to cause incorrect BAEPs results, but the pathology of higher structures such as the cochlear nuclei, the superior olivary complex, the trapezoid body, the lateral lemniscus or the inferior colliculus, characteristic for IS or MS usually cause incorrect BAEPs and HMAAT results [31]. In our study both CPAT patients had sound localization problems in the HMAAT but only one of them had incorrect BAEPs result.

In the HMAAT we found sound localization disturbances most often in the anterior and the right-sided azimuths, less often in the posterior and the left-sided ones. When we compared patients with and without auditory pathway involvement higher angle values were again present for the right-sided azimuths (45° and 90°). 8 of the 11 patients (72.7%)

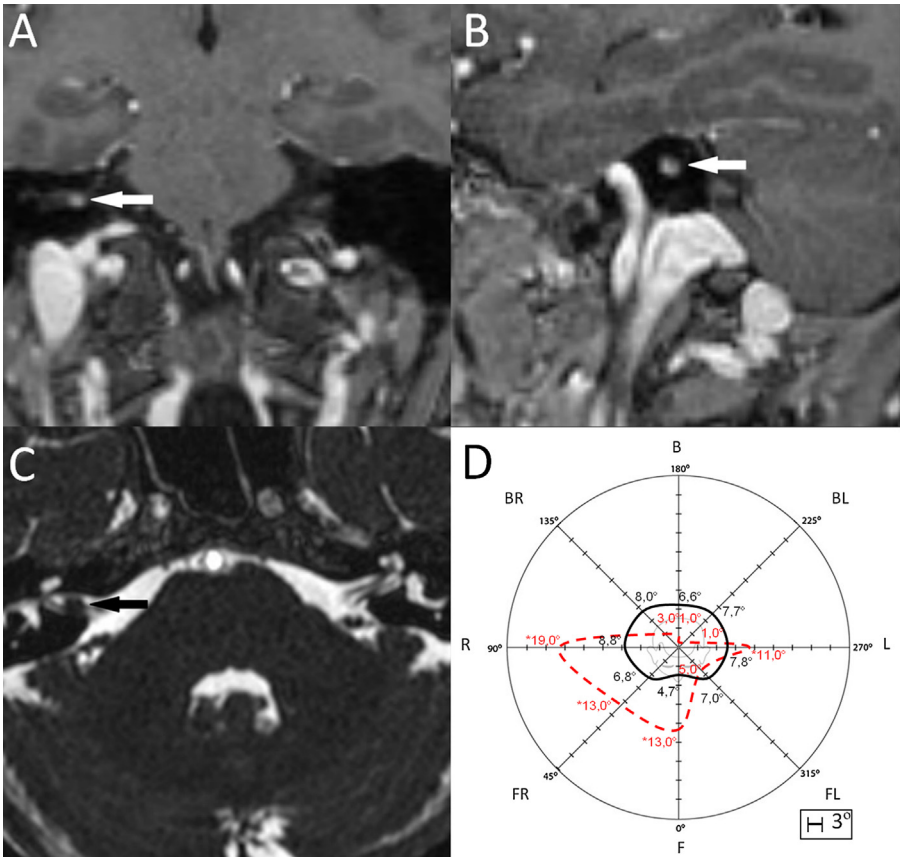

Fig. 4 – A 40-yo female patient. Magnetic resonance of a small schwannoma within the right internal auditory canal (arrows) in coronal post-gadolinium T1-weighted (A), sagittal post-gadolinium T1-weighted (B) and axial heavy T2-weighted (C) images. The HMAAT results (D). Black line – 95th percentile values for the age-matched subgroup of controls; red dotted line – abnormal results of the patient in the 0°, 45° and 90° azimuths (these are right-sided azimuths, that is the ipsilateral azimuths). F – front; B – back; R – right; L – left; FR – frontal right; FL – frontal left; BR – back right; BL – back left. Red color – actual data points for MAA angle value in a patient; black color – reference value of respective age subgroup. *MAA values exceeding 95th percentile values for the age-matched subgroup of controls. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

had right-sided lesions that could confirm the ipsilateral character of the sound localization disability.

The strongest correlation in our study was the one between the disturbance of sound localization (90° and 270° azimuth) and the volume of lesions. The strength of correlation was probably due to IS (these patients had bigger lesion volume in comparison with other patients with MS and CPAT). This strong correlation could be explained by the extensive connections of the auditory brainstem nuclei that are responsible for binaural interaction and also assure redundancy in the system. This redundancy may explain why small brainstem lesions are sometimes clinically silent [10].

We also tried to find certain correlations between the side of the sound localization disturbance and the level of the lesion in the brainstem. We hypothesized that lesions below or within the cochlear nuclei result in ipsilateral auditory – processing abnormalities detected in routine testing. In a study by Häusler et al. [2] patients with acoustic neuroma, had bilateral sound localization disturbances, mainly in 90° and 270° azimuths. However, the disturbances were always worse on the side of the tumor. Disorders rostral to the cochlear nuclei, in the region of VAS, may result in bilateral abnormalities or may be silent [10]. Lesions in the superior olivary complex and trapezoid body show a mixture of ipsilateral, contralateral, and bilateral abnormalities – Häusler and Levine [31] described an audiometrically normal 80-year-old man with trapezoid body and superior olivary comlex infarct with bilaterally impaired sound lateralization.

Lesions of the lateral lemniscus, the inferior colliculus, and the medial geniculate body may result in predominantly subtle contralateral abnormalities [10,17]. Litovsky et al. [17] reported a 48-year-old man with a small traumatic hemorrhage of the right dorsal midbrain, including the inferior colliculus, with deficits of sound localization in the contralateral hemifield to the hemorrhagic lesion. It seems that results of our study prove the abovementioned hypotheses, however, the mechanisms of sound localization coding on brainstem level remain greatly unknown [32].

Our study has obvious limitations, one of which is a small number of subjects. However, this was due to stringent

audiometric criteria, that allowed to eliminate the influence of the conductive and the sensorineural hearing loss on HMAAT results. The criteria caused the substantial reduction of eligible subjects, a situation commonly found in previous studies on patients with brainstem pathology [18,28–30]. Another limitation results from the fact that the assessment of the auditory pathway involvement may be restricted by MRI resolution and the slice thickness, which varied from 3 to 5 mm. However, we believe that meticulous analysis of the images with use of anatomical atlases, increased the accuracy of assessment of the auditory pathway involvement. The effect of any error in registration of the auditory pathway with an MR section is likely to have less effect upon interpretation when the error involves axial sections or caudal regions of sagittal sections [30]. Thus, we assessed auditory pathway involvement in multiple sections. One more limitation is the changeable size of demyelinating, stroke or tumor lesions. If the MRI is not performed at the same time as the sound localization ability testing, the results can be variable [30]. All of our patients underwent audiological testing in 2 months time on average from the head MRI and neurological diagnosis. Other authors tried to reduce this time to the maximum of 1.5 months [28]. However, in a study on ischemic stroke patients this time reached even 6 months [13].

5. Conclusions

In the presented study we analyzed anatomical and clinical factors of the sound localization ability in patients with brainstem lesions. These lesions due to IS, MS and CPAT caused disturbance of sound localization of one or both hemispaces in the HMAAT in more than 80% and incorrect BAEPs in about 50% of our patients. The biggest quantitative disturbances in the HMAAT were present in the CPAT and the MS patients. The strongest correlations were present between the sound localization disturbances in HMAAT and the volume of pathological lesions in the brainstem. We did not confirm the correlation between ipsilateral HMAAT disturbances and the brainstem pathology localized beneath the VAS, and contralateral disturbances correlating with lesions localized above this structure. Our study confirms that brainstem disorders can cause substantial sound localization deficits.

Conflict of interest

The authors declare that there is no conflict of interests regarding the publication of this paper.

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None declared.

Ethics

The work described in this article has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans; Uniform Requirements for manuscripts submitted to Biomedical journals.

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